BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 37, NO. 5 MAY 1961

CLINICAL IMPLICATIONS OF CYANOSIS*

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SEVERAL years ago a farmer, age 51, entered Bellevue Hospital in a state of partial confusion. He was weak and listless, and his thin, poorly-nourished body suggested that he was both seriously and chronically ill. His illness had started ten years earlier when he began to be troubled by breathlessness. This symptom was always related to effort; it did not occur at night; and for a long while it was not associated with other stigmata of heart and lung disease. Then one year before admission his ankles became swollen. Digitalis reduced the edema, but the fluid reaccumulated over a period of several months. A few days before admission the patient became confused and disoriented. When these symptoms failed to respond to bed rest, the man was brought to Bellevue.

The House Officer first ruled out the possibility of digitalis intoxication, then he treated the patient's congestive failure vigorously. By the end of a week this regimen had improved the man considerably; his dyspnea had subsided and his confusion had disappeared. But a puzzling

* Presented at the Fourth Annual Postgraduate Week, *Frontiers in Medicine and Surgery,* of The New York Academy of Medicine, October 25, 1960.

complication persisted: the skin and mucous membranes of the patient remained markedly cyanosed. The puzzle did not arise from a lack of causes to explain the cyanosis; it stemmed, rather, from the fact that none of the possibilities seemed adequate to account for the intense discoloration of the skin. The problem was further complicated by two points in the history. The first was that the man was an alcoholic. The second was that he had worked for many years in silos where, on several occasions, he had developed acute dyspnea while breathing the irritating fumes which rose from the mouldering hay.

Because of the unusual nature of his illness, the patient attracted much attention. He enjoyed the individual opinions of a score of doctors and the collective opinions of three conferences. Yet, when he suddenly became worse six months later, he died without the precise diagnosis having been made. At Bellevue we regard the man as one of the most curious examples of cyanosis we have encountered, and in my own mind the name of this patient and the word "cyanosis" are rather firmly linked.

Thus, when Dr. McGuinness extended his kind invitation to speak here this evening, I immediately recalled the story of this man. And I thought it might be worthwhile to use that story as a background for this presentation, by tracing the attempts which were made to unravel the patient's disease. To this end, my remarks about cyanosis will be divided into three parts: general considerations, specific causes, and —finally—frontiers, since frontiers are the themes of the presentations this week.

General Considerations

The most useful first step is to agree on a definition of "cyanosis". The word stems from the Greek and simply means "dark blue". Although more elaborate definitions have been suggested, none has been completely satisfactory. Hence, for the purposes of this discussion, "cyanosis" will be used to denote a blueness of either the mucous membranes or the skin.

The second point is that cyanosis cannot be measured. It is a subjective diagnosis and, as such, frequently controversial. Those of you who are interested in observer variability will enjoy a paper published in 1947 by Dr. Julius Comroe and Dr. Stella Botelho.[1] These investigators induced different degrees of cyanosis by administering different

hypoxic mixtures to normal subjects, and they then had platoons of physicians express opinions as to whether the subjects looked blue. The results must have disillusioned practicing physicians, because the data revealed two unexpected facts. The first was that the majority of observers were unable to detect cyanosis when the arterial saturation had fallen to 80 per cent. The second was that a quarter of the observers still could not perceive blueness when the arterial saturation lay between 71 and 75 per cent. These observations led Comroe and Botelho to conclude that the appearance of cyanosis depends on the doctor as well as on the patient, a point which sometimes goes unrecognized.

The third consideration concerns the time-course of cyanosis. In many patients the degree of blueness varies, a circumstance which further complicates the problem of deciding whether cyanosis exists.

The fourth point is of particular importance; it is that multiple factors contribute to the color of the skin. Lundsgaard,[2, 3] and later Lundsgaard and Van Slyke,[4] analyzed the various factors and decided that the thickness of the epidermis, the density of the capillaries, and the dilatation of the vessels were important determinants. They also believed that the pre-eminent factor was the concentration of reduced hemoglobin circulating in the cutaneous capillaries. Specifically, they thought that cyanosis would appear in a patient, who was otherwise normal, when the reduced hemoglobin reached a level of about 5 grams per 100 ml. of capillary blood. Since this level is related to both the arterial and venous saturations, it follows that blueness may be expected in any situation where the oxygen content of either the arterial or venous blood is lowered. It also follows that polycythemia—which increases the concentration of hemoglobin—will increase the likelihood of the appearance of cyanosis, while anemia will tend to reduce the chance of its occurrence. Although in a small series Geraci and Wood[5] were not able to demonstrate that cyanosis appeared in polycythemic patients at higher arterial saturations than in normal subjects, the approximate relation between these two variables is still worth repeating. Whether or not the appearance of cyanosis depends directly on the number of red cells, the concentration of the cells unquestionably influences the color of the skin. The same is true of the concentration of any abnormal pigment in the blood, the skin, or the subcutaneous tissues. In short, blueness depends on multiple factors, not a single one.

TABLE I—CONDITIONS CAPABLE OF PRODUCING EITHER GENERALIZED OR LOCALIZED CYANOSIS IN PATIENTS WHO HAVE NORMAL ARTERIAL SATURATIONS

1. Congestive heart failure.
2. Venous obstruction.
3. Shock.
4. Local vasomotor disturbances: acrocyanosis, Raynaud's disease.
5. Abnormal hemoglobin: methemoglobin, sulphemoglobin.
6. Abnormal pigments: silver, Evans blue dye.

How, then, do these generalizations bear on the patient whom we saw at Bellevue? He was definitely blue; the intensity of his blueness varied little with time; nothing in his story implicated a single factor as the cause of his trouble; and he was neither polycythemic nor anemic. Hence, we all agreed that the man had a serious condition, but at the outset we had little idea about its identity.

SPECIFIC CAUSES

We next turned to considering the causes of the patient's cyanosis. Several classifications of causes have been suggested, most of the schemes having been based on defined terms.[3, 6] For example, all of you have heard of "central cyanosis", "peripheral cyanosis", "hypoxic hypoxia", "anemic hypoxia", and "stagnant hypoxia". For the most part, these terms were coined more than a decade ago, before the array of tests now available for studying cyanosis had been devised. The terms are still useful, but in practice a complex classification can be replaced by three questions, which the physician can ask. The questions are:

1. Is the patient's arterial saturation normal?
2. If the saturation is low, is it because the alveoli do not oxygenate the pulmonary capillary blood properly?
3. If the saturation is low and the alveoli function properly, is the cyanosis due to the presence of channels which by-pass the alveoli and carry venous blood into the systemic circulation?

Answering these questions will lead to a diagnosis in the majority of persons who are blue.

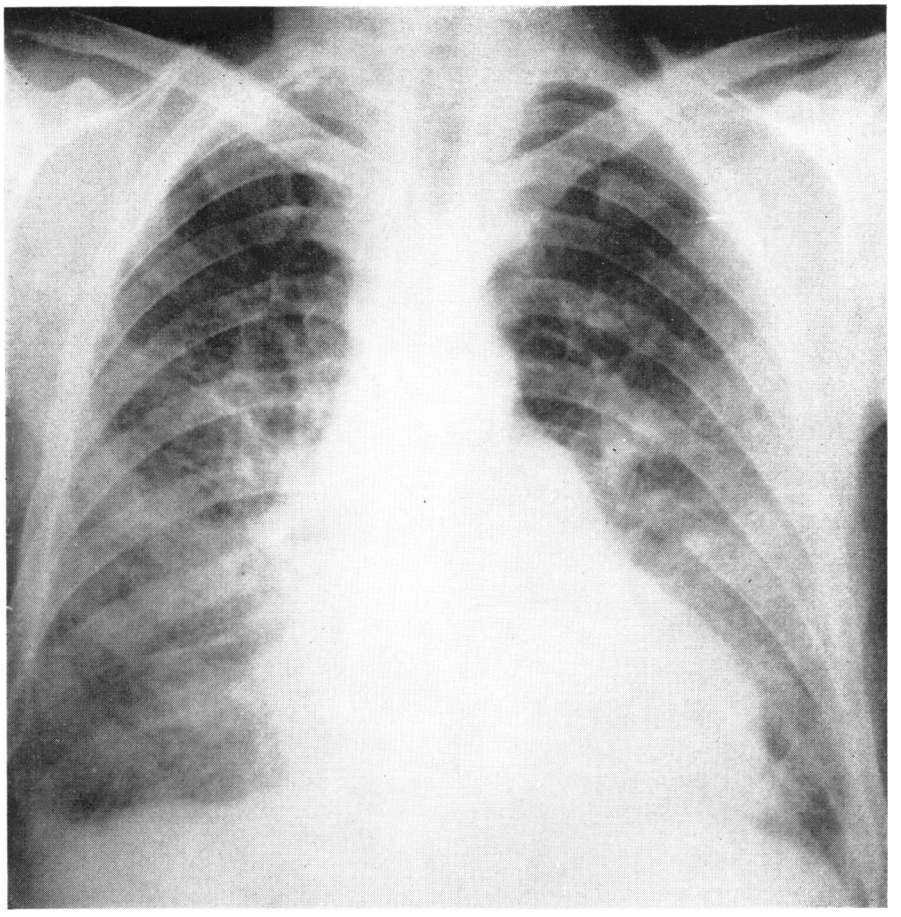

Figure 1. Chest x-ray of the patient.

The arterial saturation of our patient was abnormal. Measured on several different occasions, the level varied between 60 and 81 per cent. This, therefore, eliminated the conditions listed in Table I as the sole sources of the patient's color. The listed disorders represent both common and uncommon causes of cyanosis, and they embrace several mechanisms whereby blueness is produced. For example, a patient with either congestive heart failure or venous obstruction can have a normal arterial saturation and yet be cyanotic because the venous saturation is so low. The same is true of any patient who has a reduced cardiac output: the classic example is a patient in shock. Similarly, regional

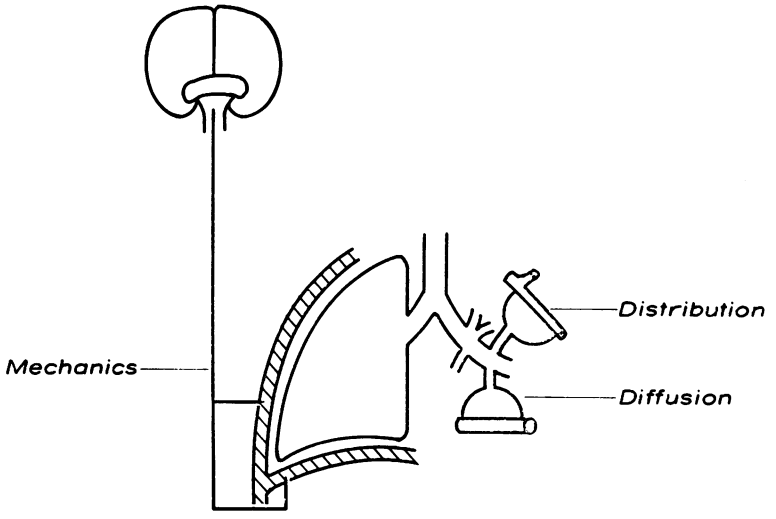

Figure 2. Parts of the respiratory process.

vasomotor disturbances, such as Raynaud's disease, can produce local cyanosis of an intense degree. Also, a man can have a normal arterial saturation and yet be cyanotic if abnormal hemoglobin or dyes circulate in his blood. Because of the current interest in blood volume measurements, the sudden appearance of cyanosis in a hospitalized patient can sometimes be traced to an earlier injection of Evans blue dye.

But our patient had arterial unsaturation, so we asked the second question, "Do the alveoli oxygenate the pulmonary capillary blood properly?" Evidence that this question might have an important bearing on the patient's illness was provided by the physical examination. The chest was hyperresonant and crackling rales were audible at the bases of the lungs. Further, the chest x-ray (Figure 1) was definitely abnormal: the alveolar areas were mottled and the hilar shadows were accentuated. Under fluoroscopy the motion of the lungs seemed adequate, the chest wall having a normal excursion and the leaves of the diaphragm moving freely despite some blunting of the right costophrenic angle.

In view of the suspicious appearance of the lung fields, we began assessing the effectiveness with which the alveoli supplied oxygen to the pulmonary capillary blood.[7] The structures important to this process are sketched in Figure 2. As shown in the drawing, the medulla, the

nerves and the respiratory muscles must be capable of supplying the lungs with about five liters of air per minute, and the volume of the lungs must be adequate to accept this supply of air. Further, the air must be distributed to alveoli contacting actively perfused capillaries. Finally, the diffusion of oxygen from alveolar air to capillary blood must proceed without impediment. These related processes are conventionally grouped under three headings: mechanics, distribution and diffusion.

In our patient the mechanics of breathing, assessed by the usual indices, seemed surprisingly good. The maximal breathing capacity was normal; the vital capacity was 80 per cent of the predicted value; the total lung capacity was only slightly diminished; and the residual volume was not enlarged. This combination argued against the presence of emphysema, one of the most popular initial diagnoses.

The distribution of blood and gas appeared to be less satisfactory. In assessing this part of the respiratory process we found that the dead space of the patient was much increased. In fact, 70 per cent of each inhaled breath did not take part in the exchange of oxygen and carbon dioxide. This indicated a gross disturbance of distribution, since in normal man the dead space constitutes only about 20 per cent of the volume of each breath.

Further, the diffusing capacity of the lungs seemed to be subnormal. Although technical difficulties precluded the possibility of calculating a specific figure, there was evidence that some sort of block impeded the exchange of gas. But what could have produced the barrier? Nothing in the history or physical examination supported a diagnosis of sarcoid, beryllosis, silicosis, disseminated carcinoma or miliary tuberculosis, the usual causes of diffusion block. It is true that the man had worked in silos and was, therefore, qualified to have either "silo-filler's disease" or "farmer's lung." Again we could not establish the presence of either condition, although these were two of the diagnoses put forth on the medical ward.

Hence our answer to the second question was partly precise and partly equivocal. On the one hand, the mechanics of breathing were so nearly normal that emphysema seemed unlikely. On the other, the defective distribution and diffusion of gases made a diffusion barrier seem the best possibility, although we had no clue regarding the underlying etiology.

TABLE II—SOURCES OF VENOUS MIXTURE

1. Congenital defects of the heart and great vessels.
2. Thebesian veins.
3. Anterior cardiac veins.
4. Bronchial-pulmonary vascular anastomoses.
5. Pulmonary arteriovenous shunts.
6. Portal-mediastinal-pulmonary vascular connections.

We turned, therefore, to the third question: "Did venous blood reach the systemic circulation through channels bypassing alveoli?" Such blood, called "venous admixture", travels through extra-alveolar pathways and thus does not participate in the exchange of gas. The pathways which can contribute to the total admixture are listed in Table II.

The first step toward proving the existence of one of the pathways is to measure the arterial oxygen content while the patient breathes oxygen. At high tensions of this gas, the blood hemoglobin is not only saturated but about 2 ml. of oxygen exist in physical solution in each 100 ml. of blood. Further, breathing oxygen minimizes the effects of malfunctioning alveoli, so that any deficit in the arterial oxygen content is chiefly due to venous admixture alone. But pitfalls may obscure the results of this test for the unwary physician. First, the oft-quoted rule that the disappearance of cyanosis on breathing oxygen rules out the diagnosis of venous admixture, is an unreliable criterion. Second, the use of an oximeter to gauge the disappearance of cyanosis during oxygen breathing may also give a misleading result. This is owing to the fact that both approaches fail to take into account the oxygen carried by the blood in physical solution; this dissolved oxygen is capable of masking a defect in the function of the alveoli.

Since our patient did not achieve full arterial saturation when he breathed oxygen, we wondered whether one of the listed pathways might be contributing to the color of the skin. The grossly enlarged heart led some physicians to suggest that the patient had a congenital cardiac defect, and, in the remote hope that the man might have a remediable lesion, Dr. Ludwig Eichna, Dr. Bertha Rader and other members of their staff performed a cardiac catheterization. Dr. Eichna

TABLE III

	Right Atrium	*Right Ventricle*	*Pulmonary Artery*	*Brachial Artery*
O_2 Saturation (%)	33	33	33	69
Presssure (mm.Hg.)	7	102/5	104/36	106/62

and Dr. Rader have kindly allowed me to publish the results shown in Table III. In patients such as this man, one searches for abnormal openings between the right and left chambers by following the course of the catheter under the fluoroscope and by examining the oxygen content of samples of blood withdrawn from various sites. While no openings were identified and no discrepancies in saturation were demonstrated, the pressure measurements were peculiar: the pulmonary and brachial arterial systolic pressures were almost identical, as can be seen in Table III. This raised a faint suspicion that even though there were no murmurs, the man might have a ventricular septal defect.

Supplementary tests, such as angiography, might have provided additional information. Another test—one which has become popular since this man was studied—entails using dye curves to detect septal defects. This technique, developed mainly through the efforts of Dr. Earl Wood, Dr. H. J. C. Swan and other members of the Staff of the Mayo Clinic,[8-10] is based on the principle depicted schematically in Figure 3. Here, a ventricular septal defect carries venous blood into the systemic circulation, and the arterial dilution curve has two peaks, rather than one.

But there was little evidence to support the diagnosis of a septal defect, so we considered the possibility that the extracardiac pathways listed in Table III were carrying venous blood around the lungs. Because of the limitations in methodology, the contributions of only a few of these channels can be individually identified. For instance, no method is available for measuring the blood perfusing anterior cardiac and Thebesian veins; this flow, however, is thought to be small. Nor can we measure the flow through bronchial-pulmonary connections which carry unsaturated blood into the pulmonary veins.

Recently, a technique has been developed to assess pulmonary arteriovenous shunt flow by using intravenous injections of solutions

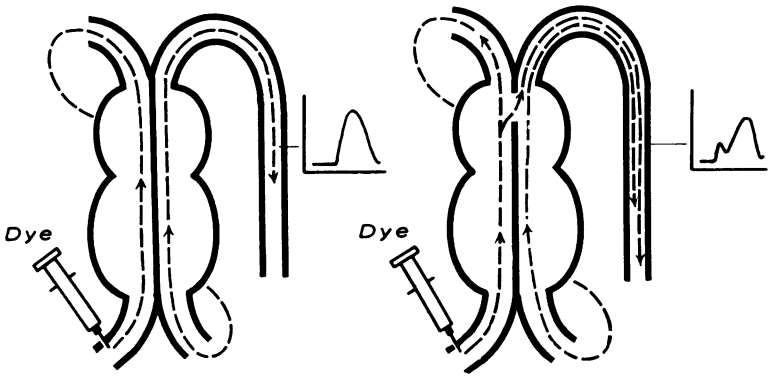

Figure 3. Technique of using dye curves to detect septal defects. Dye is injected into the venous circulation. Normal patient on the left gives an arterial dilution curve with a single peak; patient on the right has a septal defect with a right-to-left shunt and, as a consequence, his curve has two peaks.

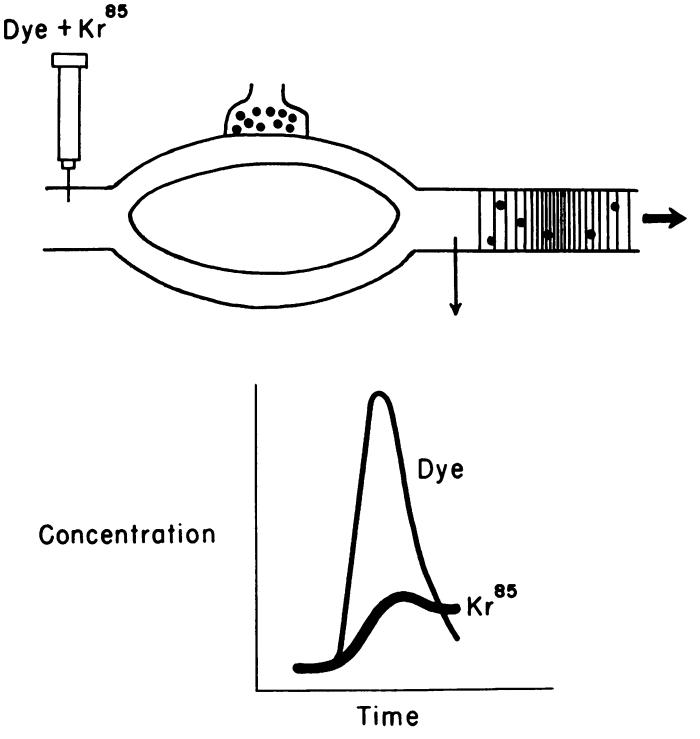

Figure 4. Use of intravenous injections of dye and Kr^{85} to detect pulmonary arteriovenous shunts.

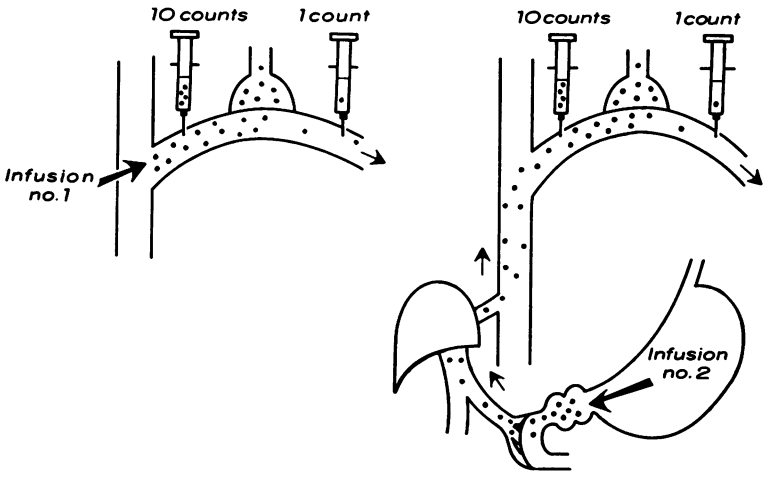

Figure 5. Infusion of Kr^{85} into the right atrium (left) and stomach (right) of a patient free of hepatic disease. For explanation, see text.

containing the inert gaseous isotope Kr^{85} dissolved in Evans blue dye.[11] The principle of the method is shown schematically in Figure 4. Blood traversing shunts retains its Kr^{85}, while blood perfusing capillaries loses its Kr^{85} into the alveoli. By comparing the amount of Kr^{85} to the amount of blue dye appearing in the brachial artery, the fraction of the pulmonary arterial blood flow perfusing shunts can be estimated. But since this technique was not available when the patient was studied, the value it might have yielded is not known.

The last pathway, seen in patients with Laennec's cirrhosis, has recently attracted much attention and could have conceivably contributed to the cyanosis in this man. McIndoe,[12] Schoenmackers and Vieten,[13] and Calabresi and Abelmann[14] have all adduced postmortem evidence for the existence of vascular connections between the portal circulation and the pulmonary veins. To test whether blood traverses this pathway in living patients, the method sketched in Figures 5 and 6 has been utilized.[11] Kr^{85} is first infused into the right atrium while samples of mixed venous and arterial blood are drawn. Later, Kr^{85} is introduced into the portal circulation by injecting a solution into the stomach through a Levine tube, and again arterial and venous samples are collected. In subjects free of liver disease (Figure 5), the lungs clear about 90 per cent of the Kr^{85} from the blood stream regardless of

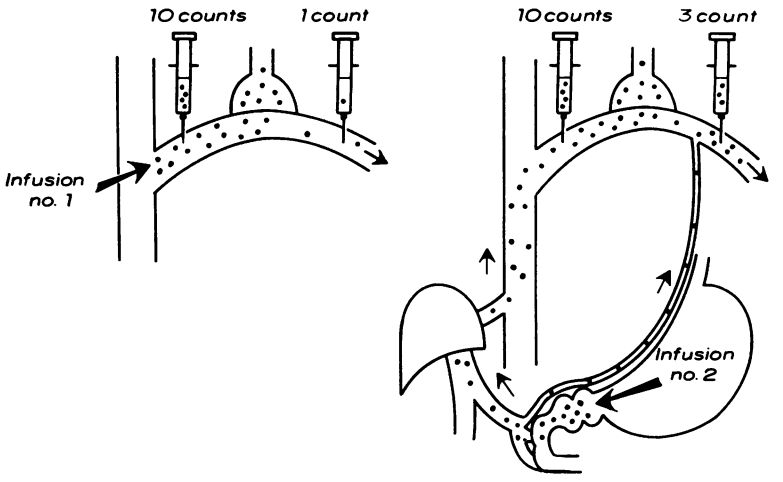

Figure 6. Infusion of Kr^{85} into the right atrium (left) and stomach (right) of a patient with cirrhosis. Postulated portal-pulmonary connections are sketched. For explanation, see text.

the route of the infusion, so that for every ten counts appearing in the mixed venous sample, only one appears in the arterial blood. But patients with cirrhosis behave differently. Whereas the ratio of ten to one obtains when the isotope is infused into the right atrium, the ratio falls to about ten to three when Kr^{85} is introduced into the stomach (Figure 6). While these results have suggested the presence of the portal-pulmonary connections sketched in the drawing, they have not revealed the magnitude of the flow which these connections carry. Even if the method had been available during the life of our patient, it would doubtless have shed little light on our problem, since it seems improbable that an arterial saturation of 60 per cent could be caused by portal-pulmonary connections alone.

This, then, was the story. The man did not have emphysema; probably he had a diffusion block; possibly he had a congenital heart defect; maybe he had some other vascular pathway which carried venous blood around the alveoli. In short, we didn't know.

Our questions were answered by the autopsy, which provided sections of lung tissue such as that shown in Figure 7. The section was stained by the Smith-Dietrich technique, and it revealed that the cells were loaded with fat which had a high phospholipid content. Hence,

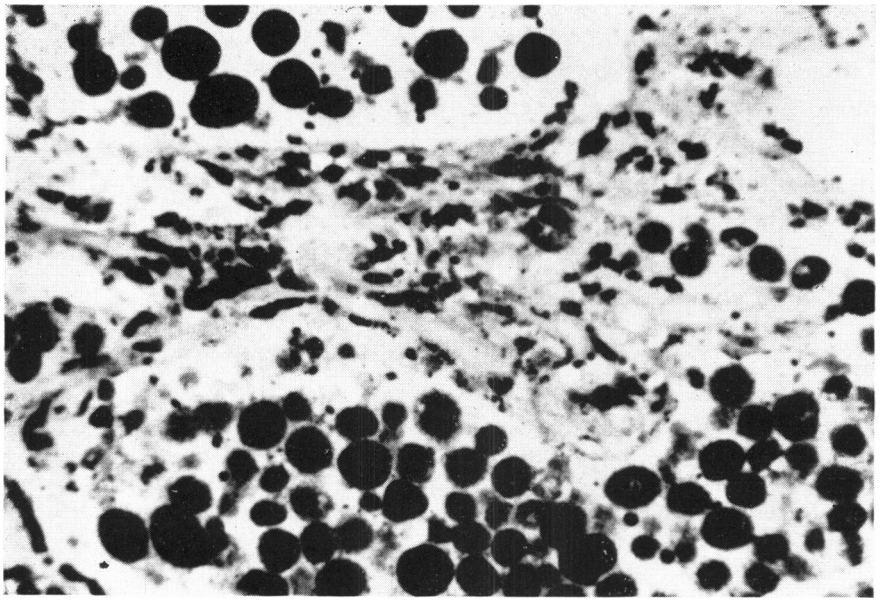

Figure 7. Section of lung tissue stained by Smith-Dietrich technique. Black globules are fat (Courtesy Dr. Marvin Kuschner).

the man had a lipoidosis of the Niemann-Pick variety, an unusual occurrence in a person his age. Abnormal tissue almost completely replaced the alveoli, and while the exact state of the lung physiology cannot be reconstructed, it seems likely that the man's primary difficulty was a diffusion defect. In addition, the gross disruption of the pulmonary architecture undoubtedly disturbed the distribution of blood and gases and may even have caused some of the pulmonary vessels to act as arteriovenous shunts.

Thus, in this man as in all other patients, cyanosis suggests one of the situations implied in the three previously mentioned questions. On the one hand, the patient may have a disorder which causes blueness in the presence of a normal arterial saturation, while on the other he may have arterial unsaturation due either to alveoli which do not function properly, or to vessels which carry venous blood around his lungs.

Frontiers

In closing, it is appropriate to mention a few frontiers of the problem of cyanosis. First, we do not have sensitive methods for resolving

venous admixture into its various components. Second, the possibility that latent arteriovenous shunts exist in the normal pulmonary circulation is still debated. Third, several diseases are particularly perplexing; among them are cirrhosis, anemia, pulmonary emboli and polycythemia vera, all of which are either known or thought to produce arterial unsaturation, and none of which is fully understood. In fact, the frontiers of the problem of cyanosis are approximately the same as those of cardiac and pulmonary diseases. Thus, these frontiers are numerous, broad, and complex.

ACKNOWLEDGEMENT

I am indebted to the members of the Third (New York University) Medical Service of Bellevue Hospital for their kindness in allowing me to discuss this patient. I owe especial gratitude to Dr. Ludwig Eichna, Dr. Bertha Rader, Dr. Marvin Kuschner, and Dr. Hugh Carroll. Also, Dr. Anne Davis is publishing a full description of the patient. She generously consented to let me review some of the features of his illness in this report.

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